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ELIXIR SULFANILAMIDE

LETTER

FROM THE

SECRETARY OF AGRICULTURE

TRANSMITTING

IN RESPONSE TO SENATE RESOLUTION No. 194
A REPORT ON ELIXIR SULFANILAMIDE-MASSENGILL

NOVEMBER 16 (calendar day, NOVEMBER 26), 1937.—Referred to the
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LETTER OF TRANSMITTAL

DEPARTMENT OF AGRICULTURE,
Washington, November 25, 1937.

Hon. EDWIN A. HALSEY,
Secretary, United States Senate.

DEAR MR. HALSEY: Respectfully submitted herewith is my report on Elixir Sulfanilamide-Massengill, requested in Senate Resolution 194 of November 16, 1937.

Sincerely,

H. A. WALLACE, *Secretary.*

REPORT OF THE SECRETARY OF AGRICULTURE ON DEATHS DUE TO ELIXIR SULFANILAMIDE-MASSENGILL

[Submitted in response to S. Res. 194 of November 16, 1937]

During September and October of 1937 at least 73 persons died as a direct result of taking the drug known as "Elixir Sulfanilamide." Twenty other persons who took the "elixir" died, but it has not yet been established that this drug was exclusively responsible. The 93 deaths occurred in 15 States, as far east as Virginia, as far west as California.

"Elixir Sulfanilamide" was manufactured and sold by the S. E. Massengill Co., of Bristol, Tenn. According to the firm's books, 240 gallons were manufactured. The entire amount has been accounted for.

Before the "elixir" was put on the market, it was tested by the firm for flavor but not for its effect on human life. The existing Food and Drugs Act does not require that new drugs be tested before they are placed on sale.

"Elixir Sulfanilamide" was first distributed commercially on September 4, 1937, and continued to October 15, 1937. The first word of deaths from an unidentified sulfanilamide preparation reached the Food and Drug Administration on October 14. On October 16 an investigator for the Administration telegraphed from Tulsa, Okla., that nine persons had died there after taking "Elixir Sulfanilamide." Seizure of all outstanding shipments was immediately ordered.

Since the Federal Food and Drugs Act contains no provision against dangerous drugs, seizures had to be based on a charge that the word "elixir" implies an alcoholic solution, whereas this product was a diethylene glycol solution. Had the product been called a "solution," rather than an "elixir," no charge of violating the law could have been brought.

Of the 240 gallons manufactured, 228 gallons and 2 pints have been seized under Federal and State laws, destroyed, collected as laboratory samples, or wasted by spillage and breakage. Eleven gallons and six pints were dispensed on prescriptions or over-the-counter sales. Of this amount, about half was consumed and caused the deaths; the other half was retrieved before consumption.

The lethal effect of the "elixir" was due to its content of diethylene glycol, which was used as a solvent in making a liquid preparation of sulfanilamide, usually administered in tablet or powder form. Sulfanilamide itself is a valuable drug, and was not responsible for the disaster.

Sulfanilamide is the name of one of a group of closely related chemicals first reported in European medical literature of 1935 to have been used for drug purposes. It has shown dramatic curative effects. Physicians in this country have been quick to recognize its far-reaching possibilities. Its use has grown to tremendous proportions. An

editorial from the Journal of the American Medical Association, attached as exhibit A, shows that sulfanilamide is potentially dangerous but that properly used it may be brilliantly successful in treating various infections.

The fatal "elixir" was rushed onto the market without adequate test to determine whether or not diethylene glycol may be safely used as a solvent for sulfanilamide, despite previously published reports in scientific literature showing that diethylene glycol might be dangerous when taken internally. A few simple and inexpensive tests on experimental animals would have quickly demonstrated the toxic properties of both diethylene glycol and the "elixir."

A typical label follows:

ONE PINT ONE PINT

ELIXIR

SULFANILAMIDE

Each fluidounce represents:
Sulfanilamide. 40 grs.

SUGGESTED FOR THE TREATMENT OF ALL CONDITIONS IN WHICH THE HEMOLYTIC STREPTOCOCCI APPEAR

Dose, begin with 2 to 3 teaspoonfuls in water every four hours. Decrease in twenty-four to forty-eight hours to 1 or 2 teaspoonfuls and continue at this dose until recovery.

[Trade-mark]

THE S. E. MASSENGILL COMPANY
Manufacturing Pharmacists
BRISTOL, TENN.-VA.

It will be observed that the preparation is a semisecret one, that the presence of diethylene glycol is not disclosed, and that no warning of danger appears.

Most of the drug was administered on physicians' prescriptions.

HOW THE "ELIXIR" WAS PRODUCED

Dr. Samuel Evans Massengill is sole owner of the S. E. Massengill Co., of Bristol, Tenn. He holds the degree of doctor of medicine, and was licensed to practice medicine in 1900. His letterhead bears the statement "Purveyor to the professions of medicine and pharmacy since 1897."

Mr. Harold Cole Watkins, chief chemist and pharmacist of the company, holds a degree of pharmaceutical chemist. Since 1900 he has been engaged as pharmaceutical, analytical, and research chemist by various firms. He joined the Massengill Co. in 1935.

For some time before putting "Elixir Sulfanilamide" on the market, the S. E. Massengill Co. had been marketing sulfanilamide in capsule and tablet form. In June 1937 the firm's salesmen reported a demand for the drug in liquid form. Near the end of July Mr. Watkins, according to his own statement, undertook the problem of finding a suitable liquid vehicle for sulfanilamide. Since sulfanilamide is insoluble in the various liquids commonly employed in making medicines he tried a number of other solvents. Diethylene glycol was found to dissolve as much as 75 grains of sulfanilamide per fluid ounce, but in that concentration it tended to separate out on chilling. Accordingly he decided upon 40 grains per fluid ounce as a stable preparation and devised the following working formula:

Sulfanilamide	pounds	58½
Elixir flavor	gallon	1
Raspberry extract	pint	1
Saccharin soluble	pound	1
Amaranth solution 1–16	pints	1½
Caramel	fluid ounces	2
Diethylene glycol	gallons	60
Water q. s	do	80

According to Mr. Watkins no tests were made to determine the toxicity of either the separate ingredients or of the finished product, or to determine by well-known methods available for the purpose whether or not the sulfanilamide decomposed in the diethylene glycol. The so-called "control" laboratory merely checked the "elixir" for appearance, flavor, and fragrance. Dr. Massengill confirmed Mr. Watkins' statement that no experimental animals were used or clinical tests of any kind made to determine either the effectiveness or the toxicity of the drug before it was put on the market.

On August 28, 1937, the formula for "Elixir Sulfanilamide" developed by Mr. Watkins was sent to the Kansas City branch of the company where 40 gallons was subsequently manufactured. In the Bristol plant an initial trial batch made consisted of 40 gallons, from which commercial distribution was begun on September 4, 1937. Subsequently two additional batches of 80 gallons each were made in this plant, most of which went into distribution.

Commercial shipments in amounts varying usually from 1 pint to 1 gallon were made, not only from the Bristol and Kansas City plants, but also from the New York and San Francisco sales branches to which supplies had been sent. The following list shows the number of such shipments:

	Shipments
From Bristol, Tenn	413
From Kansas City, Mo	190
From New York City	11
From San Francisco	19
Total	633

In addition, 208 1-ounce physicians' samples and 187 2-ounce salesmen's samples were distributed from Bristol; 276 1-ounce physicians' samples were distributed from Kansas City. Distribution of both commercial and sample lots extended over the period from September 4, 1937, up to and including October 15, 1937.

THE FOOD AND DRUG ADMINISTRATION STEPS IN

The first word of deaths from an unidentified sulfanilamide preparation reached the Food and Drug Administration on October 14, 1937, through a telephone call from a New York physician associated with a large drug manufacturing concern. He repeated advices, presumably received through professional or trade contacts, that fatalities had occurred at Tulsa, Okla.

Immediately instructions to investigate the report were issued by telegraph to the Kansas City station of the Food and Drug Administration, which is the nearest station to Tulsa. A representative of the administration arrived in Tulsa the following day. He reported by telegraph on Saturday, October 16, that nine deaths had already occurred in Tulsa, including eight children with streptococcic sore throat and one adult with gonorrhea, and that all had taken a product labeled "Elixir Sulfanilamide, the S. E. Massengill Co., Manufacturing Pharmacists, Bristol, Tenn.-Va."

Shipping records showed that the suspected "elixir" had come from a Massengill establishment in Kansas City, to which the station immediately sent inspectors. Also an inspector from the Cincinnati station, which is the nearest station to Bristol, and a medical officer from the administration's headquarters at Washington, were sent at once to Bristol.

It was found that some of the "elixir" had been made at the Kansas City branch factory and that supplies had been sent to the New York and San Francisco sales branches. Immediately inspectors from the New York and San Francisco stations were assigned to investigate distributions from these points.

It was learned that the Massengill Co., following reports of the poisonous effects of the "elixir," had sent out approximately 375 telegrams from Bristol and additional telegrams from its branch houses totaling, according to the firm's statement, some 1,100 in all, requesting the return of outstanding shipments. The texts of these wires follow:

From the Bristol office to customers, on October 15, 1937:

> Do not use elixir sulfanilamide shipped. Return our expense.

To salesmen on the same date:

> Elixir sulfanilamide discontinued. Pick up as rapidly as possible all sold in your territory.

From the Kansas City branch to jobbers, druggists, and doctors who had received the product, on October 15:

> Have withdrawn product elixir sulfanilamide. Please return unused stocks immediately.

From the New York branch to customers, on October 16:

> Return for credit all elixir sulfanilamide you have of our manufacture. We shall appreciate prompt attention.

On or about October 16, on telegraphed instructions from the Bristol office, the San Francisco branch of the firm instructed its salesmen to have outstanding stocks returned. However, investigation revealed that no attempt had been made by that branch to communicate directly with dealers and doctors.

On October 15 the Bristol office wired the New York branch:

> Discontinue sale elixir sulfanilamide. Wire all salesmen immediately. Pick up sold. Wire direct all customers sold to return stock unused.

On the same date the New York branch wired to 13 of its salesmen who were thought to have sold the "elixir," and wrote to its remaining 26 salesmen, one of whom was in Puerto Rico. Telegrams and letters were practically identical:

Discontinue the sale of elixir of sulfanilamide. Pick up and return all orders of this item previously sold. We are discontinuing immediately the manufacture of this item.

Since these telegrams and letters gave no indication of the dangerous character of the product and were not calculated to impress receivers with the emergency character of the call for returning the goods, the inspector assigned to the Bristol office insisted that the firm issue the following telegram, dated October 19, to all persons who were listed as having received shipments of the "elixir" from Bristol:

Imperative you take up immediately all elixir sulfanilamide you dispensed. Product may be dangerous to life. Return our expense.

Following similar insistence by the San Francisco, Kansas City, and New York inspectors, the branches at these points sent the following or similar telegrams to all consignees, on or about October 19:

Imperative you take up immediately all elixir sulfanilamide you may have dispensed. Product may be dangerous to life. Return all stocks our expense.

As a result of these telegrams large quantities of the "elixir" were returned to the manufacturer's establishments and there taken under local or Federal control. But the extremely dangerous character of the drug necessitated the most searching check to guarantee, as far as humanly possible, its complete apprehension. Practically the entire field force of 239 Food and Drug Administration inspectors and chemists were assigned to the work. They had the wholehearted and effective cooperation of State and local food, drug, and health authorities. As an additional aid, warnings by newspaper and radio were broadcast.

In spite of the manufacturer's telegrams many shipments were found still in dealers' hands. Innumerable prescriptions filled from these lots, as well as from shipments returned to the manufacturer, were found to have been only partly consumed by the patient and so were recovered.

The essential steps in tracing and apprehending the poisonous drug were (*a*) listing names and addresses of consignees, dates of shipment, and amounts shipped from the four establishments of the manufacturer; (*b*) following these to the primary consignees and seizing, if still intact in their possession; (*c*) if partially used, seizing the residue and following and procuring the distributed portions if not already consumed; (*d*) checking on lots reported returned to the manufacturer and definitely ascertaining whether such returned lots were intact; (*e*) if returned lots were not intact, searching for dispensed portions.

To accomplish these objectives it was necessary to supplement the information obtained from the manufacturer's shipping records and from consignees' records by contacting approximately 200 salesmen employed by the firm and consulting their records of sale and distribution, as well as the records of samples they had personally distributed. As a cross-check on the accuracy of the manufacturer's distribution lists, a very large number of inquiries were made of drug houses throughout the entire country for the purpose of ascertaining whether they might have received any shipments not included in the manufacturer's records.

The magnitude of the task of listing distributions is indicated by the fact that thousands of order slips had to be examined, one by one, in the four distributing houses and that in some cases this procedure had to be repeated in wholesale and retail drug stores to determine what redistributions had occurred. In one establishment alone, 20,000 sales slips were examined.

The task was complicated by the fact that distribution was not made exclusively on physicians' prescriptions, which normally would have recorded the name of the patient, but that over-the-counter sales were made to lay purchasers who in some cases were entirely unknown to the druggist. In some instances doctors had no record of the names and addresses of patients for whom they had prescribed, or the names recorded were fictitious.

The task of interviewing promptly the approximately 200 salesmen employed by the Massengill Co., in order to account for salesmen's samples and to check the distribution of physicians' samples and commercial shipments, presented serious difficulties in some cases. A typical instance was that of a salesman whose territory includes part of Maryland and Virginia. He was first reported to be at a hotel in Washington, D. C. He was not there. Forwarding addresses at Jackson, Mich., and in Baltimore were investigated only to learn that these were for another man of the same name. After 4 days' search, the salesman was found at University Park, Md. One salesman in Texas was thoroughly uncooperative and was put in jail by the State authorities before he decided to reveal the necessary information.

At East St. Louis, Ill., 49 prescriptions, all for colored people, were filled from two shipments. The only identification on some of the prescriptions were such notations as "Betty Jane, 9 months old" or "Mrs. Jackson (no address)." In a very few instances recipients of prescriptions bearing no identification have not yet been found, although every effort has been made to warn them by newspaper and radio. One prescription was for "Willie Smith," who was known to be on the relief rolls. There were six colored "Willie Smiths" on relief rolls, but the remainder of this prescription was obtained. One prescription was dispensed to an East St. Louis colored woman who said she had destroyed it. On questioning, it developed that she simply threw the bottle out the window into an alley. The inspector found the bottle unbroken, still containing ample "elixir" to kill any child intrigued to swallow its pink, sweet, aromatic liquid.

THE PROBLEM BEFORE PHYSICIANS AND PHARMACISTS

Most of the physicians and pharmacists involved in dispensing the "elixir" cooperated willingly and effectively in apprehending outstanding prescriptions. Typical was the attitude expressed by Dr. A. S. Calhoun, writing in the New Orleans States of October 22:

> Nobody but Almighty God and I can know what I have been through in these past few days. I have been familiar with death in the years since I received my M. D. from Tulane University School of Medicine with the rest of my class of 1911. Covington County has been my home. I have practiced here for years. Any doctor who has practiced more than a quarter of a century has seen his share of death.
>
> But to realize that six human beings, all of them my patients, one of them my best friend, are dead because they took medicine that I prescribed for them innocently, and to realize that that medicine which I have used for years in such cases suddenly had become a deadly poison in its newest and most modern form, as

recommended by a great and reputable pharmaceutical firm in Tennessee; well, that realization has given me such days and nights of mental and spiritual agony as I did not believe a human being could undergo and survive. I have spent hours on my knees, once I had done all any physician could do for his patients. I have known hours when death for me would be a welcome relief from this agony.

Thank God, the six remaining patients to whom I gave that medicine show no signs of dying as a result. It seems like a miracle to me. I have spent hours driving to see every one of them, white and Negro. I have checked and rechecked their condition several times a day. Why they are not dead like the first six who died, I do not understand. For some obscure physical reason, their bodies were able, apparently, to throw off the poisonous effects of the medicine.

It is miraculous to me. I do not understand it. But I am grateful to Almighty God. Those six deaths weigh heavily enough on my mind and heart. Six more! I shudder when I think of it as a possibility. To me those six yet living who took that elixir have been like six human beings standing under sentence of death ever since I got the warning from the pharmaceutical house that made and sold it, that it was poisonous in that form. I have lost track of how many miles I have driven, trying to counteract the results of the fatal mistake of the men who prepared that medicine.

In contrast was the attitude of a South Carolina doctor who told the inspector he had dispensed 1 pint 15 fluid ounces to three white patients and two Negroes whose names he did not reveal. He insisted that none of these patients had died. Information acquired by the inspector from other sources showed that the doctor had administered the elixir to seven patients, that three survived, that a white man, a white girl, and two Negro men had died. One of the fatal prescriptions was traced through neighborhood gossip describing the symptoms of the fatal illness of a Negro employee of a lumber mill. The inspector recognized the symptoms as characteristic of "elixir" poisoning, and through the mill superintendent found the victim's sister. She remembered that the doctor had given her brother some red medicine about October 2 or 3. She said that, in accordance with their custom, all medicines, glasses, spoons, etc., had been placed on the grave, which was about 1½ miles back in the fields. Accompanied by the Negroes, the inspector walked to the wooded knoll with its single mound of fresh earth on which lay several bottles, dishes, and spoons. One 4-ounce bottle contained about 1 ounce of the "elixir." It bore the weatherbeaten but legible prescription label of the doctor.

An inspector investigating a Georgia drugstore listed as having received 1 gallon of the "elixir" was informed that the shipment had been returned to the manufacturer at Bristol after only one lot of 6 ounces had been dispensed for one patient. Subsequent investigation showed that this patient had suffered no ill effects. But the inspector assigned at Bristol for the purpose of checking returned lots found 12 instead of 6 ounces missing from the gallon bottle returned by this druggist. Further investigation showed that two additional lots had been dispensed and had caused two deaths.

EFFECTS OF THE DRUG

The victims of the "elixir" were ill from about 7 to 21 days. They suffered intense pain. All exhibited very much the same symptoms—stoppage of urine, severe abdominal pain, nausea, and vomiting; stupor; convulsions preceded death in some cases. Many persons who took the drug discontinued its use with the onset of unfavorable symptoms and recovered. One person took as much as 7½ fluid ounces without ill effect. One child died from less than 2 fluid ounces.

The consequences of marketing this poisonous drug cannot be better revealed than by the following letter addressed to the President of the United States by a bereaved mother in Tulsa, Okla.

TULSA, OKLA., *November 8, 1937.*

President ROOSEVELT:

DEAR SIR: Two months ago I was happy and working taking care of my two little girls, Joan age 6 and Jean age 9. Our byword through the depression was that we had good health and each other. Joan thought her mother was right in everything, and it would have made your heart feel good last November to have seen her jumping and shouting as we listened to your reelection over the radio.

Tonight, Mr. Roosevelt, that little voice is stilled. The first time I ever had occasion to call in a doctor for her and she was given the Elixir of Sulfanilamide. Tonight our little home is bleak and full of despair. All that is left to us is the caring for of that little grave. Even the memory of her is mixed with sorrow for we can see her little body tossing to and fro and hear that little voice screaming with pain and it seems as though it would drive me insane. During her 9 days of illness as we sat by her bed only once did those little eyes lose their dull and unknowing look. Jean and I begged her to look and know us. A smile broke over her face and she laughed aloud with us and as quickly it vanished, never to smile and know us again.

Tonight, President Roosevelt, as you enjoy your little grandchildren of whom we read about, it is my plea that you will take steps to prevent such sales of drugs that will take little lives and leave such suffering behind and such a bleak outlook on the future as I have tonight.

Surely we can have laws governing doctors also who will give such a medicine, not knowing to what extent its danger, and then lying and stealing the prescription they wrote supposedly from a reliable drug store. I don't believe such a doctor has taken his oath in all sincerity. Our lives are not safe entrusted in the hands of such a doctor, for that was my experience to my sorrow.

In my confidence in you I am writing you and hope that you can realize a little of what I am suffering and that you will take steps to prevent such in the future for I realize also there are other homes where hearts are broken such as mine.

It is easy for people to say "Try to think that she died that others might live." It is easier to say when it doesn't strike in your own home.

Enclosed is a picture [1] of the baby I grieve for day and night. Thanking you and

Sincerely,

(Mrs.) MAISE NIDIFFER.

ACTION UNDER THE LAW

Twenty-five seizures of the "elixir" were effected under the Federal Food and Drugs Act. Many lots were seized or embargoed by local officials through action under State or city laws.

The distribution of the shipments from the four establishments maintained by the manufacturer of the "elixir" and the deaths that occurred are shown in the map [1] attached as exhibit B.

Citations are already in preparation for issuance to the manufacturer, in accordance with established procedure, calling on him to show cause why the cases should not be referred to the Federal courts for criminal prosecution.

In September 1934 and March 1937 the S. E. Massengill Co. was convicted in criminal prosecutions and paid fines for violations of the Food and Drugs Act, as recorded in notices of judgment attached as exhibit C. Also included in this exhibit is a notice of seizure of a shipment of one of this firm's drugs.

Records of the Post Office Department show that in 1929, H. C. Watkins, the Massengill Co. chemist who made the "elixir," was distributing a medicine represented to reduce weight, to bring about "perfect slenderness" and to cause the body to acquire "a trim, youthful, athletic look." On October 30, 1929, the Watkins Laboratories

[1] Not printed.

and others were cited by the Solicitor of the Post Office Department to show cause why a fraud order should not be issued. Mr. H. C. Watkins filed a stipulation with the Department, agreeing that the sale of the product would be abandoned and not resumed at any future time.

LIMITATIONS OF THE LAW

As indicated earlier in this report, the only basis of action under the Food and Drugs Act against the interstate distribution of the "elixir" was the allegation that the word implies an alcoholic solution, whereas the product was a diethylene glycol solution. The fact that the law contains no specific definition of "elixir" may be responsible for Dr. Massengill's statement in his letter to the American Medical Association, carried in the press of November 3: "I have violated no law."

Most drug manufacturers recognize a responsibility to the public far greater than that imposed by existing law. Some are known to have considered making a solution of sulfanilamide in diethylene glycol before the "elixir" was put on the market, but abandoned the idea on investigating the toxicity of the solvent. But the attitude of some drug makers is exemplified in Dr. Massengill's statement carried by the press on October 23:

> My chemists and I deeply regret the fatal results, but there was no error in the manufacture of the product. We have been supplying legitimate professional demand and not once could have foreseen the unlooked-for results. I do not feel that there was any responsibility on our part. The chemical sulfanilamide had been approved for use and had been used in large quantities in other forms, and now its many bad effects are developing.

That evidence of possible danger from the internal administration of diethylene glycol was available prior to the marketing of the "elixir" is shown by the attached exhibit D.

That a few simple tests on experimental animals would have demonstrated the lethal properties of the elixir is evident from the work reported by the American Medical Association in exhibit E. These results were confirmed independently by the Division of Pharmacology of the Food and Drug Administration in work yet unpublished.

While the "elixir" incident has been spectacular and has received much publicity, aside from the brevity of the period in which the killings occurred, it is but a repetition of what has frequently happened in the past in the marketing of such dangerous drugs as dinitrophenol, cinchophen, and other toxic substances.

It is worthy of note that, shocking as these instances have been, the actual toll in deaths and permanent injury from potent drugs is probably far less than that resulting from harmless nostrums offered for serious disease conditions. In these cases the harmful effect is an indirect one. Sick people rely on false curative claims made for worthless concoctions, and thus permit their disease to progress unchecked. It may be too late when they lose confidence in the nostrum and seek rational treatment.

RECOMMENDATIONS FOR LEGISLATION

To protect the public from drugs which, like the "elixir," are dangerous because of their inherent toxicity, it is the Department's recommendation that legislation be enacted to provide at least the following:

1. License control of new drugs to insure that they will not be generally distributed until experimental and clinical tests have shown

them to be safe for use. The definition of what constitutes a new drug should include (*a*) substances which have not been used sufficiently as drugs to become generally recognized as safe, (*b*) combinations of well-known drug substances where such combinations have not become generally recognized as safe, and (*c*) well-known drug substances and drug combinations bearing label directions for higher dosage or more frequent dosage or for longer duration of use than has become generally recognized as safe.

Exemption should be made for new drugs distributed to competent investigators for experimental work. A board of experts should be provided who will advise the Secretary of Agriculture on the safety of new drugs.

It is the Department's view that no other form of control will effectively safeguard the public from the dangers of premature distribution of new drugs. To increase the penalties for violations and to require label disclosure of ingredients would be helpful, but by no means fully adequate.

In the interest of safety, society has required that physicians be licensed to practice the healing art. Pharmacists are licensed to compound and dispense drugs. Electricians, plumbers, and steam engineers pursue their respective trades under license. But there is no such control to prevent incompetent drug manufacturers from marketing any kind of lethal potion. It should be remembered that Dr. Massengill and his chemist, Watkins, are far better equipped from the standpoint of technical training than many other persons now engaged in the manufacture of drugs.

2. Prohibition of drugs which are dangerous to health when administered in accordance with the manufacturer's directions for use. This would provide a more appropriate basis of action than that on which proceedings were instituted against the "elixir." A number of dangerous drugs are now on the market against which not even a trivial charge of violation can be made.

3. Requirement that drug labels bear appropriate directions for use and warnings against probable misuse. Much injury results from insufficient directions and from lack of warning against overdosage, or administration to children, or use in disease conditions where the drug is dangerous, or possibility of drug addiction.

4. Prohibition of secret remedies by requiring that labels disclose fully the composition of drugs. Many foreign countries now impose this requirement. Many drugs manufactured in the United States are exported to such countries under labels bearing such disclosure. The same drugs are sold to our citizens under labels that give no hint of their composition.

The physician, and the consumer who acts as physician to himself, both have a right to know what they administer.

Many poisoning cases result from choice of the wrong bottle from the home medicine cabinet, or from bottles left within the reach of small children. In such cases attending physicians are able to proceed intelligently and administer the proper antidotes or other treatment only if labels carry full disclosure of composition. Delays in obtaining this information by communicating with the manufacturer may often mean the difference between life and death.

Physicians are also handicapped in arriving at a correct diagnosis and beginning appropriate treatment when patients come to them after unsuccessful attempts at self-medication with secret remedies.

The effect of such remedies may give rise to symptoms leading to erroneous diagnosis. But even if the diagnosis is correct, the kind of treatment to be used may depend upon what the patient has been taking. Again, in such circumstances, label declaration of composition may mean the difference between life and death.

The foregoing recommendations are limited to provisions which the Department believes should be enacted to safeguard the public from the dangers of drugs of one type. That type includes the inherently toxic drugs, such as the "elixir," dinitrophenol and cinchophen. Many additional points should be considered if adequate protection is to be extended against even more widespread dangers to health and other abuses of public welfare arising from the inadequate control authorized by the present law over various other types of drugs.

EXHIBIT A

EDITORIAL, JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, OCTOBER 2, 1937, ON THE DANGER OF SULFANILAMIDE

SULFANILAMIDE—A WARNING

Seldom has any new drug introduced in medical practice aroused the enthusiasm that has developed for sulfanilamide. Much of this enthusiasm is warranted. The drug is truly remarkable, as indicated by startling results reported in the treatment of various infections. Indeed, its coming has stimulated research in pharmacology and biochemistry to a remarkable degree. Moreover, as is customary, departments of research associated with the manufacture of pharmaceutical products have already taken to the long trail of studying similar and associated preparations and derivatives to find something better or just as good which they can call all their own. When these derivatives appear for sale, the optimistic advertising departments will extol them as far superior to sulfanilamide itself. The therapeutic or toxic properties of new drugs cannot be predicted from their chemical formulas. Experience indicates that many of the new drugs will be without therapeutic advantage over the nonproprietary sulfanilamide; some may enhance such undesirable side reactions as granulocytopenia or severe damage to the erythrocytes. In Europe, similar research is being done on nitroso compounds and various derivatives. Out of the mass of developed preparations may come some drugs of merit. Until plenty of evidence is available, however, as to the virtues and dangers of such products, the medical profession may well be skeptical. Many months of investigations of the pharmacology, toxioclogy, and clinical application of new preparations under carefully controlled conditions are needed to provide evidence of therapeutic value. Some of these new compounds may have a higher chemotherapeutic index than does sulfanilamide as far as mice, for instance, are concerned. Care must be taken, nevertheless, in applying to man toxicity figures based wholly on animal experiments.

The Journal, the Council on Pharmacy and Chemistry and various individual practitioners have warned against indiscriminate use of sulfanilamide. Apparently these warnings have been insufficient. In The Journal, September 25, 11 contributions on sulfanilamide were published. Nine of these reported the occurrence of toxic manifestations, including dermatitis and photosensitization of the skin. Particularly serious are the possible dangers of granulocytopenia and sulfhemoglobinemia. The latter may sometimes go unrecognized without adequate methods of diagnosis. The complication originally called enterogenous cyanosis, thought to be due to "intestinal toxemia," has been shown to be due to the presence of sulfhemoglobin or methemoglobin in the blood.

Sulfanilamide should not be administered in association with other drugs until definite information is available as to toxic effects. Thus far only the harmlessness of sodium bicarbonate in such association seems to have been established. Magnesium sulfate and some of the coal-tar derivatives are conspicuously drugs which should not be administered concurrently.

Premature publicity for this drug has, as usual, been unfortunate. The startling news reports that the administration of sulfanilamide will "cure" gonorrhea in forty-eight hours has led to some unpleasant results. Responsibility lies considerably with pharmacists who are willing to sell dangerous drugs to anybody

over the counter.[1] In one large city, hospitals have admitted young men, with severe sulfhemoglobinemia resulting from self medication with sulfanilamide. The physician must bear in mind the potential hazards of this drug.

EXHIBIT B

(This is a map which is not printed but is held in committee files.)

EXHIBIT C

Notices of Judgment

23228. Adulteration and misbranding of fluidextract of colchicum. U. S. v. Samuel Evans Massengill, M. D. (The S. E. Massengill Co.). Plea of guilty. Fine, $150. (F. & D. no. 30317. Sample no. 5972-A.)

This case as based on a shipment of fluidextract of colchicum which was represented to be of pharmacopoeial standard but which differed from said standard since it yielded colchicum in an amount in excess of the amount provided by the United States Pharmacopoeia.

On March 20, 1934, the United States attorney for the Eastern District of Tennessee, acting upon a report by the Secretary of Agriculture, filed in the district court an information against Samuel Evans Massengill, M. D., trading as the S. E. Massengill Co., Bristol, Tenn., alleging shipment by said defendant in violation of the Food and Drugs Act, on or about July 18, 1932, from the State of Tennessee into the State of Ohio, of a quantity of fluidextract of colchicum which was adulterated and misbranded. The article was labeled in part: "Fluidextract Colchicum, U. S. P. Colchicum Autumnale * * * Standard 0.36 to 0.44 Gm. Colchicine per 100 cc * * * The S. E. Massengill Company * * * Bristol, Tenn.-Va."

The article was alleged to be adulterated in that it was sold under a name recognized in the United States Pharmacopoeia and differed from the standard of strength, quality, and purity as determined by the test laid down in said pharmacopoeia official at the time of investigation, in that it yielded more than 0.44 gram of colchicine per 100 cubic centimeters, namely, not less than 0.634 gram of colchicine per 100 cubic centimeters; whereas the pharmacopoeia provides that fluidextract of colchicum shall yield not more than 0.44 gram of colchicine per 100 cubic centimeters; and the standard of the strength, quality, and purity of the article was not declared on the container. Adulteration was alleged for the further reason that the strength and purity of the article fell below the professed standard and quality under which it was sold, in that it was represented to be fluidextract of colchicum which conformed to the standard laid down in the United States Pharmacopoeia, and was represented to contain not more than 0.44 gram of colchicine per 100 cubic centimeters; whereas it did not conform to the standard laid down in the said pharmacopoeia and contained more than 0.44 gram of colchicine per 100 cubic centimeters.

Misbranding was alleged for the reason that the statement, "Fluidextract Colchicum, U. S. P. * * * Standard 0.36 to 0.44 Gm. Colchicine per 100 cc," borne on the label, was false and misleading.

On September 17, 1934, the defendant entered a plea of guilty, and the court imposed a fine of $150.

M. L. Wilson, *Acting Secretary of Agriculture.*

27136. Adulteration and misbranding of Tablets Tinct. Aconite. U. S. v. Samuel Evans Massengill (The S. E. Massengill Co.). Plea of nolo contendere. Fine. $250. (F. & D. no. 38044. Sample no. 56057-B.)

This article contained a smaller quantity of tincture of aconite, U. S. P., than that represented on the label.

On November 16, 1936, the United States attorney for the Eastern District of Tennessee, acting upon a report by the Secretary of Agriculture, filed in the district court an information against Samuel Evans Massengill, trading as the S. E. Massengill Co., Bristol, Tenn., charging shipment by said defendant in violation of the Food and Drugs Act on or about December 12, 1935, from the

[1] Sulfanilamide has been sold under a number of brand names. The physician realizes that products marketed under brand names are exactly as dangerous as those sold as sulfanilamide. Occasionally Prontosil is mentioned as a proprietary brand of sulfanilamide. Prontosil is not sulfanilamide but is a derivative of sulfanilamide which apparently breaks down in the body to sulfanilamide.

State of Tennesee into the State of Ohio, of a quantity of an article, labeled "Tablets Tinct. Aconite," that was adulterated and misbranded.

The article was alleged to be adulterated in that its strength and purity fell below the professed standard and quality under which it was sold in that each of the tablets was represented to have the medicinal properties of 5 minims of tincture of aconite, U. S. P.; whereas in fact each of the tablets had less than 5 minims, to wit, not more than ¾ of 1 minim, of the medicinal properties of tincture of aconite, U. S. P.

It was alleged to be misbranded in that the statement, "Each tablet represents the medicinal properties of 5 mins. Tinct. Aconite, U. S. P.," borne on the bottle labels, was false and misleading in that each of the tablets was represented to have the medicinal properties of 5 minims of tincture of aconite, U. S. P.; whereas in fact each of the tablets had less than 5 minims of the medicinal properties of tincture of aconite, U. S. P.

On March 1, 1937, the defendant entered a plea of nolo contendere and the court imposed a fine of $250.

HARRY L. BROWN,
Acting Secretary of Agriculture.

24030. Adulteration and misbranding of elixir terpin hydrate and codeine. U. S. v. Five 1-Pint Bottles, et al., of Elixir Terpin Hydrate and Codeine. Tried to the court. Judgment for the Government. Decree of condemnation, forfeiture, and destruction. (F. & D. nos. 27618, 27675. S. no. 5649. I. S. nos. 38724, 38736, 38737, 42759, 42760.)

These cases involved shipments of a product, sold under a name recognized in the National Formulary, which differed from the standard laid down in that authority, since it contained no codeine alkaloid, one of the ingredients required by the National Formulary for elixir terpin hydrate and codeine, but did contain codeine sulphate, which is not found in the official article, and which is approximately 80 percent as potent physiologically as codeine alkaloid. The article contained no syrup, an ingredient required by the formulary. The label declared the presence of codeine sulphate, but failed to state that codeine sulphate is a derivative of morphine or opium.

On January 4 and 20, 1932, the United States attorney for the Southern District of New York, acting upon reports by the Secretary of Agriculture, filed in the district court libels praying seizure and condemnation of 9 pint bottles and 37 gallon bottles of elixir terpin hydrate and codeine at New York, N. Y. On March 24 and April 6, 1932, respectively, amended libels were filed. It was alleged in the libels that the article had been shipped in interstate commerce, on various dates in October, November, and December, 1931, by the S. E. Massengill Co., from Bristol, Tenn., and that it was adulterated and misbranded in violation of the Food and Drugs Act.

The article was alleged to be adulterated in that it was sold under a name recognized in the National Formulary, and differed from the standard of strength, quality, and purity as determined by the test laid down in the said formulary official at the time of investigation. Adulteration was further alleged in that the strength and purity of the article fell below the professed standard or quality under which it was sold, namely, "Each fluid ounce represents codeine sulphate 1 gr. terpin hydrate 8 grs."

The article was alleged to be misbranded in that the statement, "Each fluid ounce represents codeine sulphate one gr. terpin hydrate 8 grs.", was false and misleading; and in that the packages failed to bear a statement on the label of the quantity or proportion of codeine sulphate contained in the article, since the statement was incorrect and failed to carry the information that codeine sulphate is a derivative of morphine or opium.

Samuel E. Massengill, trading as the S. E. Massengill Co., New York, N. Y., appeared as claimant and filed answers denying the material allegations of the libels. On October 1 and 2, 1934, the cases having been consolidated and a jury having been waived, the cases were tried to the court. On November 8, 1934, the court handed down the following opinion sustaining the charges that the article was adulterated in that it failed to conform to the requirements of the formulary, and was misbranded since it failed to declare on the label that codeine sulphate is a derivative of morphine or opium, and overruling the adulteration and misbranding charges based on the alleged failure of the article to correspond with the standard declared on the label (Patterson, *district judge*):

"The Food and Drugs Act provides that any food or drug adulterated or misbranded as defined in the act and shipped in interstate commerce shall be liable to seizure and forfeiture by proceedings analogous to proceedings in admiralty. By the act, a drug is to be deemed adulterated if it is sold under a name recognized

in the United States Pharmacopoeia or National Formulary and if it differs from the standard of strength, quality, or purity therein laid down; so also if its strength or purity falls below the standard under which it is sold. Section 7; 21 U. S. C. A., section 8. A drug is to be deemed misbranded if the label on it is false and misleading; and in the case of a drug containing morphine, opium, or other specified substances or any derivative of them, it shall be deemed misbranded if the package fails to state the quantity or proportion of such substance or derivative. Section 8; 21 U. S. C. A., sections 9 and 10. There are other sorts of misbranding defined in the act of no immediate importance.

"The United States seized on two occasions a number of bottles of a liquid drug owned by one Massengill and labeled 'Elixir Terpin Hydrate and Codeine (Special). Alcohol 30%. Each fluid ounce represents: Codeine Sulphate 1 gr., Terpin Hydrate 8 grs., Glycerin q. s.' Two libels for forfeiture were filed, one for each seizure. The charge against the articles was that they were adulterated and also misbranded. Massengill appeared as claimant in each suit. The suits were tried together, and a jury waived.

"1. In the National Formulary there is a product listed as elixir of terpin hydrate and codeine. The ingredients and quantities specified for it differ materially from the ingredients and quantities set forth on the labels of the bottles seized and also from the actual contents of the bottles. The first question presented is whether the drug was adulterated because sold under a name recognized in the National Formulary but not in fact conforming to the standard required by it. The claimant's contention is that the word 'special' in the name on the label, 'Elixir Hydrate and Codeine (Special)', is an indication that the product is not the elixir of terpin hydrate and codeine defined in the formulary, and certain expert testimony in support of this contention was offered. But the question is not what the chemist or the druggist may understand by the addition of the word 'special' to the title. The Food and Drugs Act was passed as a protection to the uninformed, that they might be assured that an article purchased was what it purported to be. *United States* v. *Lexington Mill Co.*, 232 U. S. 399, 409; *United States* v. *Coca Cola Co.*, 241 U. S. 265, 276. Certainly the average consumer would not be put on guard that a compound called 'elixir terpin hydrate and codeine (special)' was not the elixir of terpin hydrate and codeine listed in the formulary. The word 'special' might well signify to him merely that the ingredients were especially pure or that the product was manufactured with special care. If a manufacturer wishes to use a National Formulary name for a nonconforming product, it is his duty to give the public unmistakable notice that in its composition there has been a departure from the formula given in the formulary.

"The Regulations for Enforcement of the Food and Drugs Act, adopted by the Department of Agriculture, have an appropriate provision. Regulation 7 (b) provides: 'A drug sold under a name, or a synonym, recognized in the United States Pharmacopoeia or the National Formulary which does not conform to the standard of strength, quality, or purity for the article as determined by the test laid down therein shall be labelled with a statement to the effect that the drug is not a United States Pharmacopoeia or National Formulary article * * *.'

"This regulation is interpretive and explanatory of the statute, not an attempted addition, and there is no doubt of its validity. See *United States* v. *Antikamnia Co.*, 231 U. S. 654. The mere word 'special' is not a statement that the product bearing a formulary name is not a formulary article. I am of opinion that the drug was adulterated in that it was sold by a name recognized in the National Formulary but varying from the standards there laid down.

"2. The second question is whether the drug was misbranded for not stating on the container that codeine sulphate is a derivative of opium or morphine. That codeine is a derivative of opium or morphine is undisputed. The presence of codeine sulphate was shown by the label, but it was not stated that codeine sulphate is a derivative of opium or morphine. The act, section 8, declares that a product containing morphine or opium, or any derivative must bear a statement of the quantity or proportion of the substance or derivative. In the Antikamnia case, supra, the point was squarely raised whether it was a sufficient compliance merely to name the derivative or whether the manufacturer was required to go further and to state of what substance the derivative was. The court construed the statute as putting on the manufacturer the double duty. In the case of a drug containing acetphenetidin, a derivative of acetanilid, he was called upon to state on the package that the article contained acetphenetidin and that this was a

derivative of acetanilid. The rule is applicable here. The packages under seizure did not bear any notice that codeine is a derivative of opium or morphine. They were therefore misbranded.

"3. The final question is whether there was adulteration or misbranding on the score that the contents of the bottles did not correspond with the declarations on the labels. The labels stated that each ounce contained 1 grain of codeine sulphate and 8 grains of terpin hydrate. There was testimony by Government chemists that on analyses there was more terpin hydrate than the quantity declared and less codeine sulphate. On the other hand, there was testimony that when compounded the products had precisely the quantities specified on the label; and there was testimony that the test for terpin hydrate is not a satisfactory one. The variations found by the Government chemists, taken as a whole, are not wide, and I am not prepared to say that they are beyond the zone of experimental error and tolerance in manufacture. The burden of proof is on the United States, and the proof does not establish adulteration or misbranding by reason of discrepancy between the quantities set forth on the labels and the actual contents of the bottles.

"There will be a decree of forfeiture for adulteration and misbranding. Findings and conclusions in conformity with this opinion may be submitted."

On December 3, 1934, judgment of condemnation was entered and the product was ordered destroyed.

M. L. Wilson, *Acting Secretary of Agriculture.*

EXHIBIT D

[Reprinted from The Journal of Pharmacology and Experimental Therapeutics, Vol. XLII, No. 3, July 1931]

The Pharmacology of Ethylene Glycol and Some of Its Derivatives in Relation to Their Chemical Constitution and Physical Chemical Properties

By W. F. Von Oettingen and E. A. Jirouch, from the Department of Pharmacology, School of Medicine, Western Reserve University, Cleveland, Ohio

* * * * * * *

PHARMACOLOGICAL ACTION

The toxicity (table 2, column 1) of the glycols was determined approximately by subcutaneous injection in white mice. The results shown in table 3 indicate that butyl ethylene glycol is by far the most toxic; the ethylene glycol ranging next; diethylene glycol, the two ethyl ethers and ethyl ethylene glycol acetate being less toxic, and 1–4 dioxan having a very low toxicity. With all the compounds the site of the injection showed more or less marked irritation, and necrosis was observed in some instances.

The systemic action (table 2, column 2) of the compounds was studied in frogs. Doses of 1 cc of a 25 percent aqueous solution were injected into the lymph sac of frogs of about 30 grams body weight. Ethylene glycol and diethylene glycol produced marked central depression, twitching of the muscles, and finally spastic extension which could not be completely removed by decapitation and pithing of the spinal cord, and which was therefore peripheral at least in part. * * *

Because hemoglobinuria and nephritis are observed in ethylene glycol poisoning in animals and in men, the compounds were injected subcutaneously in rats, in doses of from 2.5 to 5.0 cc per kilogram of a 50 percent aqueous solution, and the kidneys submitted to Dr. H. Goldblatt, of the Department of Pathology, for the microscopic examination. All showed acute nephrosis. Large doses (10 cc per kilogram) of all the compounds and smaller quantities (2.5 cc per kilogram) of butyl ethylene glycol also showed marked filling of the intracapsular spaces and of the tubules with blood, in addition to degenerative processes. This indicates that all the substances are apt to produce more or less marked pathological changes of the kidney. The question whether the other compounds used in this study produce an increased excretion of oxalic acid, as observed after the administration of ethylene glycol by Bachem (11), P. Mayer (12), and J. Pohl (13) was not investigated. The animals used in this series showed a central depression

similar to that observed in frogs. For the rats, as for the mice, butyl ethylene glycol was found to be the most, and 1–4 dioxan the least, toxic.

* * * * * * *

The inflammatory action (table 2, columns 4 a and b) was tested in rabbits by instillation of one drop of the pure material into one eye, using the other as control. All compounds produced hyperemia of the conjunctiva, most marked by ethyl ethylene glycol acetate, 1–4 dioxan, and butyl ethylene glycol.

* * * * * * *

The effect of the glycols on the excised skeletal muscle was investigated with the same arrangement, except that the muscle, instead of the nerve was immersed in the solution to be tested. Solutions of 25 percent were used, since higher dilutions of some of the glycols had little or no effect. It was found that all of the preparations depressed the muscular response to stimulation of the nerve fiber. This depression was least with ethylene glycol and ethyl diethylene glycol, more marked with diethylene glycol, ethyl ethylene glycol and 1–4 dioxan, and practically immediate and complete with ethyl ethylene glycol acetate and butyl ethylene glycol. In these experiments it was found that some of the compounds developed rigor of the muscle in different degrees, so that they may be divided in three groups: Ethyl ethylene glycol and ethyl diethylene glycol developed no rigor; ethylene glycol and diethylene glycol produced some rigor; and ethyl ethylene glycol acetate, butyl ethylene glycol and 1–4 dioxan caused very marked rigor.

* * * * * * *

The action of the glycols on smooth muscles was studied with the excised rabbit intestine (table 2, column 12) using the Magnus arrangement under strict control of the hydrogen ion concentration of the bath. It was found that 1–4 dioxan (1 : 300), diethylene glycol (1 : 300), and ethylene glycol (1 : 150) had only a very slight depressing effect on the intestine, the last being somewhat less effective. * * *

The effect of the compounds on the heart muscle (table 2, column 11) was studied by perfusing the frog heart with the Green cannula, and changing the perfusion fluid from exactly adjusted Mariotte bottles. Ethylene and diethylene glycol concentrations of from 1 to 2 percent produced only a very slight depression of the frog heart, the latter perhaps somewhat less than the former. * * *

All the compounds, therefore, caused more or less marked depression of the cardiac muscle with a tendency towards auriculoventricular block. The effect of the two glycols could be reversed by washing with Ringer solution, indicating that no irreversible reaction like the precipitation of proteins was involved. This was not possible with those compounds which precipitate proteins, with the exception of 1–4 dioxan.

The effect of the glycols on the peripheral blood-vessels was studied with the Trendelenburg frog perfusion method. Dilutions of 1 to 4 percent did not show any effect in the numerous experiments; higher concentration usually reduced the perfusion flow, preceded by a slight vasodilatation.

The action of the compounds on the blood-pressure was studied in rabbits under light ether anesthesia, with intravenous injection of 50 percent solutions of the glycols. All preparations produced a fall of blood-pressure, presumably by cardiac or central depression. Butyl ethylene glycol was the most effective, and 0.5 cc per kilogram of the 50 percent solution proved fatal.

CONCLUSIONS

Ethylene glycol and its derivatives, diethylene glycol, ethyl diethylene glycol, ethyl ethylene glycol, ethyl ethylene glycol acetate, 1–4 dioxan, and butyl ethylene glycol, depress the muscular and nervous tissue, have hemolytic properties, and produce more or less marked local irritation.

[Reprinted from The Journal of Pharmacology and Experimental Therapeutics, vol. 59, no. 1, January 1937]

Studies on the Physiological Effect of Diethylene Glycol

II. Toxicity and Fate

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[Received for publication September 4, 1936]

Notwithstanding the fact that Bachem (1) and Mendel (2) suggested several medicinal uses for ethylene glycol twenty years ago, it is only within recent years that any of the glycols have been seriously considered pharmacologically or proposed for practical employment in products for human use. Ethylene glycol, diethylene glycol, and propylene glycol are the three compounds which have received most attention. Results of some observers indicate that the toxicity of ethylene glycol is of a rather low order both acutely and chronically (1, 3, 4, 5, 6, 7); however, this belief is not unanimous (8, 9, 10, 11). Propylene glycol is considered to have a toxicity definitely lower than ethylene glycol as observed in both acute and chronic experiments (10, 11, 12, 13). Despite its proclaimed (14, 15, 16, 17), albeit severely challenged (18, 19), superiority as a substitute for glycerin in cigarette manufacture, little, strangely enough, has been published concerning the toxicity of diethylene glycol. This unfortunate lack of fundamental information prompted the studies herein reported in which attempts have been made to establish:

1. The toxicity of diethylene glycol, both acute and chronic, for laboratory animals.
2. The fate of this material in the organism, particularly in regards to the possible formation of oxalic acid.

The diethylene glycol used was of the commercial grade and was obtained from the Carbide and Chemical Corporation.

STUDIES UPON ACUTE TOXICITY

The acute toxicity of diethylene glycol was determined for both rats and rabbits employing several modes of administration. Adult white rats and adult rabbits of mixed varieties were employed and were maintained upon a standard diet (Pruina) both before and after the material had been administered; the only interruption being a twenty-four-hour starvation period prior to those instances of administration by mouth. Water was always allowed ad libitum. Usually five animals were used for each dose level, and the minimal lethal dose (M.L.D.) was selected as the smallest quantity of diethylene glycol which killed approximately 60 percent of the animals. Although death occurred usually within a day or so after administration of fatal amounts, all experiments were continued for two weeks. The symptoms of intoxication, characterized by a general depression were essentially the same as those noted by Hanzlik et al. (5) for ethylene glycol. The results of these acute toxicity experiments are listed in table 1.

The M.L.D. values obtained for diethylene glycol with rats by intramuscular and intravenous injection indicated that its acute toxicity is about one-half that of ethylene glycol and twice that of propylene glycol according to the toxicities of these latter compounds as reported by Hanzlik and his co-workers (5, 12). Seidenfield and Hanzlik (12) have noted that ethylene glycol and propylene glycol have approximately the same toxicity for rabbits by intramuscular and intravenous injection; in comparison our results show that diethylene glycol is about twice as toxic to rabbits as ethylene glycol and propylene glycol. von Oettingen (6), from a limited number of tests (four animals), approximated the minimal fatal dose for diethylene glycol to be 5 cc. per kilogram body weight when given by subcutaneous injection to mice; this is about one-third the value which we secured with rats.

[1] Associate Pharmacologist, Bureau of Chemistry and Soils, United States Department of Agriculture, at Stanford University Medical School, San Francisco, California.

TABLE 1.—*Toxicity of diethylene glycol for rats and rabbits*

Rats				Rabbits			
INTRAMUSCULAR INJECTIONS							
Dose per kilogram body weight	Number of animals	Number died	Mortality	Dose per kilogram body weight	Number of animals	Number died	Mortality
cc			*Percent*	*cc*			*Percent*
2	5	0	0	3	5	1	20
4	5	0	0	4	5	4	80
6	5	0	0	6	3	3	100
7	5	4	80	8	3	3	100
8	5	4	80	10	3	3	100
9	5	5	100				
10	5	5	100				
Intramuscular M. L. D.=7 cc.				Intramuscular M. L. D.=4 cc.			
INTRAVENOUS INJECTION							
3	5	0	0	1	5	0	0
4	5	2	40	2	5	3	60
5	5	4	80	3	5	3	60
6	4	4	100	4	5	4	80
				6	3	3	100
Intravenous M. L. D.=5 cc.				Intravenous M. L. D.=2 cc.			
SUBCUTANEOUSLY				**ORALLY**			
10	5	0	0	10	5	0	0
15	5	3	60	15	5	5	100
20	5	5	100	20	5	4	80
				50	5	5	100
Subcutaneous M. L. D.=15 cc.				Oral M. L. D.=15 cc.			

STUDIES UPON CHRONIC TOXICITY

Of major importance in determining the practicability of employing any substance for human use are its physiological effects following continued administration in small, acutely subtoxic amounts for rather prolonged periods of time. For the purpose of shedding light upon this question, white rats of weaning age were divided into eight groups of five each; six of these groups were given as their drinking water varying concentrations of diethylene glycol, and for comparison, one group was similarly fed glycerin. The general appearance, the food and liquid consumption, the fatalities, and the growth curves of these treated animals were compared with similar observations upon a control group receiving distilled water. All the rats were fed upon the standard diet of Osborn and Mendel. Table 2 and figure 1[1] demonstrate the results that were obtained in this experiment which was in progress for 100 days.

[1] Not printed.

TABLE 2.—*The effect of the addition of diethylene glycol and glycerin to the drinking water of white rats* [1]

(100 days)

Experiment	Fatalities		Average weight July 6, 1935	Average weight October 15, 1935	Weight change	Average daily intake of material (per kilogram body weight)
	Number	Days				
			Grams	*Grams*	*Percent*	*cc.*
1. Control	None		63	256	+306	
2. 10 per cent diethylene glycol	All	8	59			5.60
3. 3 per cent diethylene glycol	All	9	52			7.80
4. 1 per cent diethylene glycol	One	3	60	287	+378	0.926
	One	16				
5. 0.3 per cent diethylene glycol	One	3	54	317	+487	0.243
6. 0.1 per cent diethylene glycol	One	42	58	271	+370	0.091
7. 0.03 per cent diethylene glycol	One	33	64	248	+287	0.0025
8. 10 per cent glycerin	One	41	62	287	+363	6.98

[1] Five rats in each group.

Records of the food and water consumption of the animals carried through the 100-day experiment showed no appreciable differences among any of the groups. These experiments suggest, first, that certain small concentrations of diethylene glycol might slightly enhance the rate of growth of white rats; and second, that glycerin, in a concentration which in the case of diethylene glycol proved rapidly fatal, actually maintained the growth rate at or slightly above that of normal controls. These observations upon glycerin are in keeping with the studies by Johnson, Carlson, and Johnson upon the nutrient effect of glycerin (20). At the termination of 100 days final observations were made and the surviving animals sacrificed for autopsy studies. Dr. F. L. Apperly, Professor of Pathology of this institution, reported all vital organs to appear normal except the spleens of the rats receiving 1 percent diethylene glycol. Initial studies upon these rats indicated abnormal splenic deposits of pigment; subsequently, it was found that these accumulations did not give the characteristic stain for iron. Further studies are now being made to determine the nature and significance, if any, of these splenic changes.

The fatalities which occurred among those animals receiving 10 percent glycerin and concentrations of diethylene glycol of 1 percent or less, appeared to be due to extraneous factors rather than to the glycerin or diethylene glycol ingested. Fatalities from the higher concentrations of diethylene glycol probably were due, in part, to a deficient water consumption because of the unpalatability of such solutions. Control experiments in which a series of rats were maintained for ten days, without fatalities, on the same water consumption as those receiving these high concentrations of diethylene glycol, demonstrated that water deprivation alone could not account for the fatalities observed with the 10 percent solution of diethylene glycol. In one experiment six immature rats were given 10 percent diethylene glycol in their diet, instead of in their water, with the result that four died within 10 to 35 days and the remaining two within 70 days. Here again voluntary starvation, resulting from the unpleasant taste imparted to the diet by the diethylene glycol, might have played a part.

THE FATE OF ORALLY ADMINISTERED DIETHYLENE GLYCOL

In a study of the physiological effect of any substance its ultimate fate in the animal organism is of much interest and importance. No studies have been reported in the literature bearing upon the metabolism or mode of elimination of diethylene glycol, although mention is made that ethylene glycol, a closely related compound, is converted partially into oxalic acid and this then eliminated by way of the urinary tract (21). This observation suggested to us the following experiments in which the urine and feces of both dogs and rats, to which diethylene glycol had been given orally, were examined at intervals for the presence both of oxalic acid (22) and unchanged diethylene glycol (23). The results with rats are given in table 3, from a study of which it becomes apparent that both diethylene glycol and glycerin may increase the amount of urinary oxalic acid. It is note-

worthy that gram for gram glycerin appears to be definitely less "oxalic acid forming" than diethylene glycol.

When 2 cc per kilogram body weight of diethylene glycol was fed to two dogs, it effected no appreciable change in the amount of oxalic acid present in the urine over a period of several days. The urine remained negative for albumin, sugar, and blood. However, it appears that from 40 to 70 percent of the orally administered diethylene glycol can be recovered from the urine. Only a trace was found in the feces. One dog was given 2 cc of diethylene glycol orally per kilogram body weight every day over a period of one week. Although there were wide fluctuations in the oxalic content in the urine, one is led to believe that even this rather large amount of diethylene glycol does not lead to the formation of any appreciable amount of oxalic acid in the dog. In this case the highest value obtained was 79.6 mgm of oxalic acid in a twenty-four-hour specimen of urine. In comparison, the value obtained during the control period was approximately 30 mgm.

CONCLUSIONS

In terms of cubic centimeters per kilogram body weight, the acute minimal fatal dose of diethylene glycol for white rats is, by intramuscular injection, 7 cc; intravenously, 5 cc; subcutaneously, 15 cc; and orally, 15 cc. For rabbits the minimal fatal dose is, by intramuscular injection, 4 cc; intravenously 2 cc.

TABLE 3.—*Oxalic acid in urine of normal rats and those receiving diethylene glycol and glycerin in their drinking water*

(20-day interval)

Number of rats	Drug	Amount of drug per day per kilogram	Total oxalic acid found	Oxalic acid per day per kilogram
		Grams	*Mgm.*	*Mgm.*
4	Control		6.93	0.34
3	Diethylene glycol 1.00 percent	0.660	20.16	1.17
4	Diethylene glycol 0.30 percent	0.190	13.02	0.51
4	Diethylene glycol 0.03 percent	0.016	13.02	0.67
2	Glycerin 10 percent	12.100	15.33	1.33

Rats maintained on a standard diet and receiving concentrations of diethylene glycol of 1 and 0.3 percent in their drinking water showed a slight enhancement in growth. Concentrations of 0.1 and 0.03 percent gave growth curves practically identical with the normal controls. Likewise, the growth of rats receiving a 10 percent solution of glycerin was as good as that of the controls. The ingestion of diethylene glycol in concentrations of 3 and 10 percent proved rapidly fatal.

In the rat both diethylene glycol and glycerin lead to an increase in urinary oxalic acid, although it appears that, quantitatively, glycerin is definitely less prone to do so.

In the dog, diethylene glycol fed in the amounts reported herein provoked an insignificant increase in the urinary oxalic acid, much of the drug being eliminated unchanged in the urine.

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EXHIBIT E

[Special article from the American Medical Association Chemical Laboratory]

The following reports on the chemical and pharmacologic examinations of Elixir of Sulfanilamide-Massengill are issued under the auspices of the A. M. A. Chemical Laboratory. In addition there are included reports of certain necropsies and a summary of reported deaths up to and including Friday, October 29.

PAUL NICHOLAS LEECH,
Director, A. M. A. Chemical Laboratory.

ELIXIR OF SULFANILAMIDE-MASSENGILL

CHEMICAL, PHARMACOLOGIC, PATHOLOGIC, AND NECROPSY REPORTS; PRELIMINARY TOXICITY REPORTS ON DIETHYLENE GLYCOL AND SULFANILAMIDE

I. INTRODUCTION

On Monday, October 11, telegrams were received from Dr. James Stevenson, president of the Tulsa County Medical Society, and from the Springer Clinic of Tulsa, stating that six deaths had occurred following the administration of Elixir of Sulfanilamide-Massengill, all cases having in common the pathologic condition of complete anuria. The telegrams inquired concerning the composition of the Elixir of Sulfanilamide-Massengill. In response, information was telegraphed that no product of the S. E. Massengill Company stands accepted by the Council on Pharmacy and Chemistry and that the Council had recognized no solution of sulfanilamide. The reason for the latter statement is that the Council is not in position to accept a solution of sulfanilamide until there is adequate evidence that it is both stable and does not contain toxic material in the doses recommended. The A. M. A. Chemical Laboratory immediately sent for specimens of Elixir of Sulfanilamide-Massengill. Two specimens were received from Tulsa, Okla., of the same solution which, it was stated, had been given to patients. A telegram was sent to the S. E. Massengill Company asking for the composition of the product. The firm gave the composition with the request that it be accepted confidentially. With this clue the Laboratory immediately tested the first preparation that was received. Information was telegraphed to Dr. H. A. Ruprecht of the Springer Clinic of Tulsa, suggesting the presence of diethylene glycol as the causative factor, the presence of which was confirmed by the Laboratory in the specimens examined. Original specimens were also obtained on the open market in Tulsa and a gallon of the elixir was ordered from the manufacturer. This was shipped promptly. Preliminary animal experiments were also made which indicated diethylene glycol as the toxic agent. A report of deaths in East St. Louis, Ill., was obtained from Dr. O. E. Hagebusch, pathologist at St. Louis. The composition of several specimens of Elixir of Sulfanilamide-Massengill appeared to be the same; the number of deaths in Tulsa had increased and reports from St. Louis of additional deaths indicated that the episode was not simply one of local character. The editor of The Journal then released a general warning to the public through the daily papers and over the radio. This warning was issued Monday, October 18, based on the editorial which appeared in the October 23 issue of The Journal, at the earliest possible moment after the facts were established.

Since then the headquarters group of the American Medical Association has had much assistance and cooperation from Dr. E. M. K. Geiling and Dr. Paul R. Cannon of the University of Chicago, and Dr. J. Howard Brown, Dr. Perrin Long, and Dr. E. K. Marshall, Jr., of the Johns Hopkins University, from Mr.

W. G. Campbell, chief of the U. S. Food and Drug Administration, and from Mr. J. O. Clarke, chief of the central division of the U. S. Food and Drug Administration. By close cooperation between the government and the American Medical Association, reports of deaths were immediately checked by both agencies. Furthermore, the government traced every shipment of Elixir of Sulfanilamide-

ONE GALLON ONE GALLON

ELIXIR

SULFANILAMIDE

Each fluidounce represents:
Sulfanilamide, 40 grs.

SUGGESTED FOR THE TREATMENT OF ALL CONDITIONS IN WHICH THE HEMOLYTIC STREPTOCOCCI APPEAR

Dose, begin with 2 to 3 teaspoonfuls in water every four hours. Decrease in twenty-four to forty-eight hours to 1 or 2 teaspoonfuls and continue at this dose until recovery.

[Trade-mark]

THE S. E. MASSENGILL COMPANY
Manufacturing Pharmacists
BRISTOL, TENN.-VA.

Label of gallon bottle of Elixir of Sulfanilamide-Massengill. The presence of diethylene glycol was not declared on the label. The dosage recommended should be noted, particularly the last statement "and continue at this dose until recovery." This phrase is tragically ironical in view of the number of deaths reported.

Massengill. Wherever any material had been dispensed from a bottle, efforts were made to find out to whom it had been administered and to give adequate warning in case the patients were still alive. Acknowledgment is also made to Dr. H. A. Ruprecht and Dr. I. A. Nelson of the Springer Clinic, Tulsa, who furnished the first complete statement of the postmortem examinations, to Dr. Darwin B. Childs of the Childs Clinic, Tulsa, who forwarded to the A. M. A. Laboratory specimens of the Elixir of Sulfanilamide originally dispensed, and to Dr. O. E. Hagebusch of St. Louis for forwarding his results.

II. Chemical Examination of Elixir of Sulfanilamide Massengill

E. W. Schoeffel, Ph. D., H. R. Kreider, Ph. D., and J. B. Peterson, Ph. D., Chicago

A bottle stated to contain Elixir of Sulfanilamide-Massengill, shipped by Dr. Darwin B. Childs, of Tulsa, Okla., was submitted to the A. M. A. Chemical Laboratory for examination. The bottle bore the name of the Quaker Drug Company, Rexall Drug Stores of Tulsa.

The bottle contained approximately 50 cc of a reddish, somewhat viscous liquid, having an aromatic odor resembling raspberry and anise, a sweet taste, and resembling glycerin in general physical character. The specific gravity of the substance was 1.1247 at 23 C. The surface tension was 53.8 dynes per centimeter and the index of refraction was 1.442 at 23 C.[1] A portion of the material was subjected to high vacuum distillation 10^{-6} mm (distillation range 70.95 C.) most of the distillate coming over at 75 C. After removal of water, the distillate amounted to approximately 72 per cent by volume of a clear, viscous liquid

[1] Compared with water 72 at 22.5 C.

having an index of refraction, surface tension, and boiling point the same as that for a known specimen of pure diethylene-glycol (purchased on the open market). The residue was found to consist of sulfanilamide, with small amounts of soluble saccharin, and coloring material such as amaranth or similar dye. The odor resembled anise and raspberry. A trace of alcohol was indicated. The residue when examined by microchemical means was found to consist essentially of sulfanilamide.[2] When the latter was subjected to fractionation and tested by means of the Kofler microchemical melting point apparatus, the fractions were all found to give essentially the same melting point, showing that the sulfanilamide had not decomposed in this solution.

Spectrographic examination failed to reveal the presence of such poisonous substances as lead, bismuth, mercury, and arsenic. Quantitative examinations yielded the following:

	By Volume
Diethylene glycol (approximately)	72 percent [3]
Sulfanilamide (approximately)	10 percent Weight/Volume
Water (approximately)	15.6 percent

Chemical examinations were also made on material from the original bottles from Tulsa and on material from a gallon bottle sent by the manufacturer. The resultant figures based on these determinations corresponded closely with the figures given above.

ANALYTICAL PROCEDURE

A measured amount is subjected to high vacuum distillation between 10^{-6} or 10^{-7} mm of mercury using a fractionation attachment and an all glass ground joint apparatus. The outside bath should not exceed 130 C. The boiling of the liquid begins at room temperature (25) suggesting a small amount of low boiling material. With the rise of the inside thermometer to 30 C. the receiver is changed. It contains some of the aromatic flavor substances (probably esters, ethanol, etc.). Between 30 and 65 C. most of the water comes over into the CO_2-acetone cooled receiver. With the use of a Tesla coil the end of the distillation of the water is followed up. As soon as the bright bluish discharge of the hydrogen color disappears the receiver is changed again (temperature of the distillation flask between 45 and 65 C.). The thermometer now goes up rapidly to 95 and comes back to 75 C. Again the receiver is changed. At 75 the liquid comes over at a moderate rate. From now on until the end the receiver is changed two times more following the drop in the rate of flow. The distillation is interrupted and the complete dry material is dissolved in as little boiling water as possible. On cooling, crystallization sets in. The crystalline mass is triturated with a small amount of ice water and sucked dry on an outside ice packed Buchner funnel. The mother liquid gives on evaporation a second yield of crystals. The dry crystalline material containing some of the dye and saccharin is successively extracted with absolute peroxide free ether in a continuous extractor followed by dry absolute amyl alcohol, which dissolves the sulfanilamide. The mother liquors of the fractions are evaporated and again recrystallized. All the crystalline fractions are subjected to melting point determinations to check the purity of the sulfanilamide. No decomposition products were obtained at the end of this preliminary report. Further work is in progress.

Conclusions.—From the foregoing examination it appears that Elixir of Sulfanilamide-Massengill is essentially a mixture containing approximately 9 to 10 Gm of sulfanilamide dissolved in 100 cc of a solution consisting of diethylene glycol 72 percent by volume and water 15.6 percent by volume, to which had been added a small amount of soluble saccharin, coloring such as amaranth or similar dye, flavoring resembling raspberry and anise, with an extremely small amount of reducing substances. This is in close agreement to the statements of the manufacturer that elixir of sulfanilamide contains 40 grains of sulfanilamide in one ounce of fluid and that the diethylene glycol approaches 75 percent of the volume.

[2] Sulfanilamide is the name adopted by the Council for the product para-amino-benzene-sulfonamide. It was introduced into the United States under the proprietary term Prontylin, a brand of sulfanilamide manufactured by the Winthrop Chemical Company. It should not be confused with Prontosil, which may be considered a derivative of sulfanilamide. The word Prontosil unfortunately has been used to describe several substances. Prontosil Album is used in some foreign countries as a proprietary name for sulfanilamide.

[3] In the different specimens examined, the diethylene glycol content varied from 70 to 75 percent by volume.

Contribution from the A. M. A. Chemical Laboratory.

"SYNTHETIC" ELIXIR

A synthetic preparation was also prepared for the purpose of pharmacologic investigation (this is the material referred to in the reports of Dr. E. M. K. Geiling and Dr. Paul R. Cannon which follow). The synthetic preparation consisted of diethylene glycol 75 per cent by volume, sulfanilamide 10 per cent weight/volume, 0.2 per cent soluble saccharin, and 0.2 per cent cochineal, and water to make 100 cc. This product was compared by means of the refractive index and surface tension and specific gravity with (*a*) the specimen reported on in the foregoing paragraph, (*b*) the contents of an original pint bottle of Elixir of Sulfanilamide-Massengill and (*c*) the Elixir of Sulfanilamide-Massengill received directly from the manufacturer. The determinations on the index of refraction, specific gravity, and surface tension of the several mixtures indicated that they were similar.

III. Preliminary Report of Toxicity Studies on Rats, Rabbits, and Dogs

following ingestion in divided doses of diethylene glycol, elixir of sulfanilamide-massengill, and "synthetic" elixir

E. M. K. Geiling, M. D., Julius M. Coon, A. B., and E. W. Schoeffel, Ph. D., Chicago.

Toxicity experiments were carried out on rats, rabbits, and dogs on the following substances:

1. Pure diethylene glycol.
2. Pure sulfanilamide.
3. Elixir of Sulfanilamide-Massengill.
4. "Synthetic" elixir of sulfanilamide compounded by the A. M. A. Chemical Laboratory with pure substances in approximately the same proportions as found in the Massengill elixir (see Chemical Laboratory report).

Our experiments were devised to determine:

1. The toxic and lethal doses of each of the substances when given in relatively small doses three times daily. This information seems particularly necessary since we were not able to find any data in the literature on this specific point.
2. Our experiments were further planned with the hope of being able to reproduce in healthy experimental animals, in about the same time, the clinical and pathologic picture as presented by patients who had taken fatal doses of the Elixir of Sulfanilamide-Massengill.
3. Through our experiments we hoped to discern the toxic ingredient in the Massengill elixir.

All animals were healthy adults of both sexes and had free access to food and water. The drugs were administered by stomach tube in the dosages stated in the tables. The doses selected ranged from apparently nontoxic to surely fatal ones.

From table 1 it will be seen that rats were given diethylene glycol in doses ranging from 0.5 to 4 cc., Elixir of Sulfanilamide Massengill [4] in doses of from 0.625 to 3 cc., and "synthetic" elixir in doses of from 2.66 to 3 cc. per kilogram of body weight three times daily. Most animals receiving the 0.5 cc. doses survived for eight days in apparently good health. A few, however, were beginning to show ill effects at the time of writing. About 20 per cent of the animals receiving 1 cc. of diethylene glycol or Massengill elixir have died. All animals receiving doses of 2 cc. or more of any one of the foregoing died in from two to five days with a terminal anuria. The following is an average clinical picture as seen in rats: After about the fourth dose the animal's fur becomes ruffled, there seems to be increased thirst and diuresis, food is refused, later urine excretion becomes scanty, finally the animal lies on its side, respirations increase in rapidity and depth and anuria sets in, followed by coma and death. Rabbits present essentially the same picture (table 2) but seem to be more sensitive than rats. Dogs, too, behave similarly (table 3), but the dosage cannot be accurately determined because the animals vomit after the administration of both diethylene glycol and the elixirs.

[4] In the experiments here reported the doses are larger than those used by human beings. The doses were selected to produce death in animals in about the same time and with the same symptomatology as occurred in the human beings taking the Massengill elixir. Experiments are now in progress with doses lower than 0.5 cc. per kilogram given three times daily. These experiments are indicated in view of the fact that Haag and Ambrose reported that rats succumbed when from 5 to 10 per cent of diethylene glycol was administered in the drinking water. Holck and Carlson found that rats succumbed after nine days when 4 per cent of diethylene glycol was given in the drinking water (unpublished data which we are permitted to quote).

From the Department of Pharmacology, University of Chicago.
Dr. C. W. Muhlberger, Mr. J. O. Austin, and Mr. A. Rodaniche gave valuable assistance.

Thus far we have found rats and rabbits to be more satisfactory experimental animals for this purpose than dogs.

Experiments were also performed in which sulfanilamide alone was administered by stomach tube to twelve dogs in divided doses of 0.2 Gm. per kilogram three times daily, for eight doses. At the end of this period the animals were divided into three equal groups. A, B and C. In group A two animals, dogs 2 and 4, were killed in order to see whether any significant pathologic changes had occurred in the kidneys or liver (see pathologic report). Dog 2 of group A had convulsions after the sixth dose of sulfanilamide alone but recovered. At necropsy no marked liver or kidney injury was seen. Dog 4 had no untoward reactions after administration of the sulfanilamide and showed no striking pathologic change at necropsy. The remaining two are still receiving sulfanilamide in 0.2 Gm. doses three times a day and are showing no untoward effects. Group B is receiving Massengill elixir three times daily in doses containing 0.2 Gm. of sulfanilamide. Two animals in this group refused food after the second dose; the third dog ate but vomited and the fourth ate and retained the food. Group C is receiving the "synthetic" elixir three times daily in doses containing 0.2 Gm. of sulfanilamide. In this group, two dogs refused food, the third ate but little and vomited, and the fourth ate and retained food after the second dose. The animals in both groups B and C that refused food are obviously sick at present.

Two additional dogs are receiving diethylene glycol alone in divided doses in an amount comparable to that of the diethylene glycol in the elixirs. One dog began vomiting after the second dose and at present he is moribund. The other animal began vomiting after the fifth dose and is showing weakness and tremors of the hind legs. Observations on these animals are being continued and a more detailed report will be forthcoming.

A similar experiment was carried out on sixteen rats, all of which received 0.25 Gm. per kilgram of sulfanilamide three times daily for seven doses. At the end of this period the animals were divided into four equal groups. Two rats of group 1 were killed for pathologic study and the other two continued on the same treatment of sulfanilamide. Group 2 received 2.5 cc. of Elixir of Sulfanilamide-Massengill per kilogram; group 3, 2.5 cc. of "synthetic" elixir per kilogram; group 4, 1.9 cc. of diethylene glycol per kilogram. All animals were dosed three times daily with the amount per kilogram mentioned. At the end of the fourth day all but three rats in groups 2, 3, and 4 were dead and these are expected to die on the fifth day. The two rats remaining in group 1 are apparently normal. The clinical course and the gross pathology were essentially similar in all the animals of groups 2, 3, and 4. Anuria was uniformly present. This experiment indicates clearly that it is the diethylene glycol and not the sulfanilamide which is the toxic agent.

TABLE 1.—*Data obtained from rats treated three times daily with various doses of diethylene glycol, Elixir of Sulfanilamide-Massengill and "synthetic" elixirs, and sulfanilamide*

Drug	Dose per kg. three times a day	No. of rats	Total no. of doses	Total amount of drug given per kg.	Deaths	
					Number	Percent
Diethylene glycol	0.5 cc	4	24	12.0 cc	0	0
	1.0 cc	5{3	24	24.0 cc	1	33.3
		{2	13	13.0 cc	1	50
	2.0 cc	7{4	7	14.0 cc	3	75
		{3	8	16.0 cc	3	100
	2.25 cc	4	8	18.0 cc	4	100
	3.0 cc	3	7	21.0 cc	3	100
	4.0 cc	2	5	20.0 cc	2	100
Elixir of Sulfanilamide-Massengill	0.625 cc	4	24	15.0 cc	1	25
	1.25 cc	3	24	30.0 cc	0	0
	2.50 cc	3	10	25.0 cc	2	66.6
	2.66 cc	4	9	24.0 cc	4	100
	3.0 cc	4	7	21.0 cc	4	100
Synthetic elixir	2.66 cc	4	8	21.3 cc	4	100
	3.0 cc	7{4	8	24.0 cc	4	100
		{3	7	21.0 cc	3	100
Sulfanilamide	0.25 Gm	2	24	6.0 Gm	0	0
	1.0 Gm	2	13	13.0 Gm	0	0
H_2O controls	5 cc	2	24	120.0 cc	0	0

Comment: The rats were kept in cylindric 12-inch cages in groups of from two to four: these cages were placed on 12-inch funnels and the urine flow was observed in order to determine onset of anuria; food and water were available at all times.

A series of rats were also given diethylene glycol and the two elixirs of sulfanilamide in single large amounts of 5, 10, and 15 cc per kilogram by stomach tube. After forty-eight hours all the rats of the 15 cc doses were dead. After three days all the rats on the 10 cc dose of the two elixirs had died, but only one of the three on the diethylene glycol was dead. All rats on the 5 cc dose of the three preparations are seemingly well after five days (they will be killed for pathologic study). This series is too small at present to warrant any definite conclusions. We are, however, prompted to remark that it is possible that if the kidneys and the liver are rapidly injured by a large critical dose (10 cc) of diethylene glycol, the sulfanilamide, especially in large amounts, may not be eliminated or detoxified and may have an injurious action on other tissues. In this way sulfanilamide may then be regarded as having an additive toxic effect. This is suggested as a possible explanation for the fact that some of the rats on the 10 cc amounts of diethylene glycol survived, while the animals on the elixirs succumbed. Additional experiments will have to be made to settle this point, which we believe to be interesting but not in conflict with our view that it is the diethylene glycol which is the important toxic factor (1) in the Elixir of Sulfanilamide-Massengill when given to human subjects in the amounts recommended on the label, and also (2) to our experimental animals when given in divided smaller doses. We are planning to repeat the foregoing experiments and also will give a large single amount of diethylene glycol, to be followed by a large single amount of sulfanilamide, accompanied by chemical determinations.

TABLE 2.—*Data Obtained from Rabbits Treated Three Times Daily with Various Doses of Diethylene Glycol, Elixir of Sulfanilamide-Massengill and Sulfanilamide*

Cage No.	Number of Rabbit	Sex	Weight, Kg.	Drug	Dose per Kg., T. i. d.	Total Dose T. i. d.	Total Number of Doses	Total Amount of Drug Given per Kg.	Total Amount of Drug Given	Time of Onset of Symptoms	Symptoms in Order of Appearance	Time of Death
1	1	♀	2.7	Diethylene glycol	0.5 cc	1.35 cc	20	10.0 cc	27.0 cc	72 hrs	Loss of appetite, lassitude, diuresis, increased respiration, symptoms progressed slowly until death.	213 hrs.
2	2	♀	2.6	Diethylene glycol	1.0 cc	2.6 cc	8	8.0 cc	20.8 cc	40 hrs	Loss of appetite, diuresis, weakness, increased respiration, anuria, coma, death.	61 hrs.
2	2B	♂	2.4	Diethylene glycol	1.0 cc	2.4 cc	8	8.0 cc	19.2 cc	36 hrs	Loss of appetite, diuresis, weakness, increased respiration, anuria, coma, death.	65 hrs.
3	3	♂	2.4	Elixir of sulfanilamide Massengill.	0.67 cc	1.6 cc	20	13.4 cc	32.0 cc	60 hrs	Slight loss of appetite, slight weakness; symptoms progressed slowly until death.	176 hrs.
4	4	♂	2.75	Elixir of sulfanilamide Massengill.	1.34 cc	3.7 cc	8	10.7 cc	29.6 cc	36 hrs	Same as in cage 2	58 hrs.
4	4B	♀	2.6	Elixir of sulfanilamide Massengill.	1.34 cc	3.5 cc	6	8.0 cc	21.0 cc	30 hrs	Same as in cage 2	53 hrs.
5	5	♀	2.35	Elixir of sulfanilamide Massengill.	2.0 cc	4.7 cc	6	12.0 cc	28.2 cc	30 hrs	Same as in cage 2	48 hrs.
5	5B	♂	3.2	Elixir of sulfanilamide Massengill.	2.0 cc	6.4 cc	5	10.0 cc	32.0 cc	30 hrs	Same as in cage 2	43 hrs.
6	6	♂	2.5	Sulfanilamide	0.2 Gm	0.5 Gm	20	4.0 Gm	10.0 Gm	36 hrs	Pallor in ears	Rabbit well after 7 days.

Comment: All rabbits were kept in well cleaned metabolic cages with water and food available; all doses were given by stomach tube.

TABLE 3.—*Data Obtained from Dogs Treated Three Times Daily with Diethylene Glycol, Elixir of Sulfanilamide-Massengill and Sulfanilamide*

Number, Age, Sex, and Race of Dog	Weight, Kg.	Drug	Dose per Kg., T. i. d.	Total Dose T. i. d.	Total Number of Doses	Total Amount of Drug Taken per Kg.	Total Amount of Drug Taken	Time of Onset of of Symptoms	Symptoms in Order of Appearance	Time of Death	Comment
1[1] 10 mo. male police?	11.3	Diethylene glycol.	1.5 cc.	16.9 cc.	6	9 cc.	101.4 cc.	20 hrs.	Weakness in hind legs, drunken gait, general lassitude, loss of appetite, increased respiration, diuresis, vomiting, thirst, anuria, coma, muscular tremors, spasms, delirium (barking), death.	86 hrs.	Kept in cage 8′×8′ with free access to food and water; removed to metabolic cage after 62 hrs. to observe development of anuria.
Dogs 1 and 2 were litter mates.											
2 10 mo. male police?	11.5	Elixir of sulfanilamide-Massengill.	2 cc.	23 cc.	6	12 cc. elixir (9 cc diethylene glycol, 1.2 Gm sulfanilamide).	138 cc.	20 hrs.	Same as above except death followed convulsions after feeding of milk by stomach tube; autopsy revealed no milk in bronchi.	62 hrs.	Kept in metabolic cage until death; cage kept clean; animal had free access to food and water.
3 20 mo. male terrier.	8.1	Sulfanilamide.	0.2 Gm.	1.62 Gm.	6	1.2 Gm.	9.7 Gm.	24 hrs.	No loss of appetite, slight general lassitude with rapid and complete recovery after ceasing the administration of sulfanilamide.		On the 6th day this dog weighed 9.5 Kg, a gain of 1.4 Kg. since the beginning of the experiment.

[1] Dr. Lillian Eichelberger of the Lasker Foundation, the University of Chicago, kindly made the following determinations on the blood from this animal, obtained at death:

*p*H	6.93.	Total protein	61.75 Gm per liter of serum.
Chloride	74.2 mM per liter of serum.	Nonprotein nitrogen	1.562 Gm per liter of serum.
Sodium	143 mM per liter of serum.	Albumin	36.21 Gm per liter of serum.
Potassium	13.6 mM per liter of serum.	Globulin	25.53 Gm per liter of serum.
$\frac{A}{G}$	1.42.	Water	90.57%.

Note the low *p*H and the high nonprotein nitrogen and potassium. The changes in blood chemistry are proof of the terminal uremia in our experimental animals. Through the courtesy of Prof. H. Gideon Wells, director of the Otho S. A. Sprague Institute, the University of Chicago, Dr. Carl Marberg is cooperating with us in a more detailed study of the fate of diethylene glycol in the animal body and the changes induced in the blood chemistry following ingestion of the drug. Renal and liver function tests will also be carried out on animals treated with diethylene glycol. More complete studies of the rate of elimination of sulfanilamide when administered as the elixir will be carried out.

Mr. Millberg, of our department, made numerous differential blood counts on animals receiving sulfanilamide alone, Elixir of Sulfanilamide-Massengill, "synthetic" elixir, and pure diethylene glycol. He did not find evidence which would indicate agranulocytosis.

We are privileged to say that Dr. Herbert O. Calvery, chief pharmacologist of the Food and Drug Administration, Washington, D. C., and his staff are conducting experiments which are in general accord with our own observations. Their results will be published in detail.

There are, of course, many other ramifications of this problem which have not been touched on in this preliminary report.

SUMMARY AND CONCLUSIONS

1. Our experiments thus far warrant the belief that diethylene glycol is the toxic agent in the Elixir of Sulfanilamide-Massengill examined, because experimental animals given diethylene glycol alone exhibit essentially the same clinical course and pathologic changes in the kidney and liver as do those treated with similar doses of the Elixir of Sulfanilamide-Massengill or a "synthetic" elixir containing the ingredients and in the same proportion found in the Massengill preparation by analysis. There are, of course, individual and species differences. Thus far we have found the rat and the rabbit more satisfactory subjects than the dog because with them emesis is not a complicating factor.

2. Sulfanilamide alone if given in doses of 0.2 Gm. per kilogram three times daily does not prove fatal to rats, rabbits, or dogs after eight or more divided doses. However, if sulfanilamide is given in this dosage in the form of Elixir of Sulfanilamide-Massengill or in the "synthetic" elixir, it proves fatal to experimental animals and presents a clinical and pathologic picture closely resembling that reported for the human cases in which death occurred after ingestion of the Massengill elixir.

3. Although animals receiving sulfanilamide in doses of 0.2 Gm. per kilogram three times daily did not succumb, several of them had convulsions. Six animals (two dogs and four rats) were killed after having received eight or more divided doses of the drug. None of them had anuria, nor did they exhibit the renal and hepatic changes found in animals treated with either the Massengill or the "synthetic" elixir (see report of pathologic observations). While we do not believe that the sulfanilamide had any important part in the intoxications resulting from the elixir of sulfanilamide, one must not overlook the possible damage to tissues that may result when sulfanimalide is administered to experimental animals or to human beings with impaired renal function. This point is being investigated.

4. Our experiments emphasize the importance of administering drugs in divided doses to experimental animals when it becomes necessary to know whether or not a drug has cumulative effects. Errors resulting from an oversight of this important pharmacologic principle may be costly in human lives.

We can confirm the finding of Haag and Ambrose [5] that the ingestion of 15 cc. of diethylene glycol per kilogram in a single dose by stomach tube proves fatal to rats. This figure, however, is no index of the toxic and possible fatal effects of the drug, if administered in small divided doses, especially since neither the fate nor the mechanism of detoxification is known. This substance possibly produces injury to certain cells at a rate faster than the repair processes take place; hence each succeeding dose may be adding insult to injury.

[NOTE.—After this article went to press a communication was received from Dr. E. K. Marshall, Jr., too late for inclusion in this report. In this communication he discussed the results in his experiments to date in reference to diethylene glycol, Elixir of Sulfanilamide-Massengill, and sulfanilamide. In general his experiments show that sulfanilamide alone is not responsible for elixir deaths. Large doses of sulfanilamide administered to rats and dogs revealed no functional kidney damage.—P. N. L.]

[5] Haag, H. B., and Ambrose, A. M.: J. Pharmacol. & Exper. Therap. 59: 93 (Jan.) 1937.

IV. Pathologic Effects Following the Ingestion of Diethylene Glycol, Elixir of Sulfanilamide-Massengill, "Synthetic" Elixir of Sulfanilamide and Sulfanilamide Alone

Paul R. Cannon, M. D., Chicago

Preliminary studies have been made of organs from dogs, rats, and rabbits given toxic doses stated to be Elixir of Sulfanilamide-Massengill, "synthetic" elixir of sulfanilamide, and diethylene glycol. The present report deals particularly with animals that died or were killed in a moribund state after ingestion of varying amounts of these materials. The general appearances at necropsy were as follows: The kidneys were swollen, with tense capsules and bulging, bloody surfaces, containing, in some instances, small areas of recent hemorrhage. The cortices were swollen and were usually pale. The heart was dilated and the body as a whole showed marked acute generalized passive congestion. The liver was frequently mottled and bloody but was not greatly enlarged. Pulmonary edema or bronchopneumonia was present. Clear fluid was occasionally present in the peritoneal and pleural cavities. The urine was clear and pale yellow; the gastrointestinal tract appeared essentially normal. The leptomeningeal veins were distended and the brain was tenser than usual, with, in some instances, an increase in subdural spinal fluid.

Microscopically, the most marked changes observed thus far have been in the kidneys and liver. In the former there is an intense hydropic degeneration of epithelium of the convoluted tubules, so marked that the lumens are obliterated and the normal structure is greatly altered. Albumin and hyaline casts are present within the lumens of both convoluted and collecting tubules. In some animals the epithelium of the convoluted tubules is necrotic and the cells have disappeared. The collecting tubules are relatively unchanged, although fat stains show varying degrees of fatty degeneration. The glomerular tufts are shrunken, although their capillaries are filled with blood. Albumin is also present in many of the glomerular spaces. Leukocytes are inconspicuous. The arteries, arterioles and venules appear normal.

Sections of livers show hydropic degeneration of hepatic cells, most marked around the centers of the lobules. Fatty changes are present but are not as noticeable in the areas of hydropic degeneration as at the borders of the hydropic areas. Necrosis of liver cells is not severe, although there is some shrinkage of nuclei, pyknosis, and nuclear fragmentation. Leukocytic infiltration is minimal.

A few sections from the lungs show marked congestion, edema and bronchopneumonia. The myocardium appears essentially normal, although fat stains in some instances show an early fatty degeneration. Other organs have not been examined microscopically as yet, nor have the tissues from animals receiving nonfatal doses of diethylene glycol.

The general picture is that of a severe chemical nephrosis with intracellular edema of most of the epithelial cells of the convoluted tubules, resulting in tubular obstruction by compression and by the intraluminal formation of casts. The pathologic picture is essentially similar in the three species of animals, whether given the Elixir of Sulfanilamide-Massengill, the "synthetic" elixir of sulfanilamide or diethylene glycol alone. This intracellular edema in the kidneys leads to internal disorientation of cells of the convoluted tubules and offers an explanation for the tubular obstruction, anuria, uremia, and death. Whether this intracellular change is due to cellular anoxia, with consequent intracellular edema, necrosis, fatty degeneration, and cellular desquamation, or whether it is due to hygroscopic properties of diethylene glycol are questions that must await further investigation.

These changes in the kidneys and liver are not due to sulfanilamide alone. We have examined sections from two dogs and four rats given sulfanilamide in divided doses, with toxic manifestations in one dog. The microscopic changes are slight, consisting of moderate fatty degeneration in some of the collecting tubules of the dogs, but minimal in the rats. The livers of both dogs and rats showed no hydropic degeneration and practically no fatty degeneration. There is but little question, therefore, that the severe chemical nephrosis of the dogs, rats, and rabbits is due to diethylene glycol alone. We cannot say, however, that under conditions of anuria, with retention of sulfanilamide in the blood stream, some tissue damage by sulfanilamide may not be added to that of diethylene glycol.

From the Department of Pathology, the University of Chicago.
Dr. H. G. Wells gave valuable counsel.

We have had the opportunity to examine organs from five persons who died in or near St. Louis after ingestion of Elixir of Sulfanilamide-Massengill. There is a striking similarity between the pathologic changes in the kidneys and livers in these cases and in those of the experimental animals given Elixir of Sulfanilamide-Massengill, the "synthetic" elixir, or diethylene glycol alone. The most striking changes in the human cases are hydropic degeneration of the convoluted tubules with desquamation of epithelium, fatty degeneration, tubular necrosis, hemorrhage, and obstruction of tubules by casts. In one case there is also marked recent infarction with hyaline thrombi in many of the smaller arteries. The lobular hydropic degeneration of hepatic cells is also a prominent feature in the livers from these patients.

The accompanying photomicrographs show the characteristic pathologic changes in the kidneys and livers of rats, dogs, and rabbits given Elixir of Sulfanilamide-Massengill, "synthetic" elixir, or diethylene glycol. Figures 1, 2, 3, 4, and 5 show the hydropic degeneration of epithelium of the convoluted tubules; figure 6, the lobular hydropic degeneration of hepatic cells in the liver. These are all from frozen sections of formaldehyde-fixed tissue stained with hematoxylin and eosin with a magnification of 260 diameters.

Conclusion.—There is a marked similarity in the pathologic picture in animals and in man following the ingestion in divided doses, toxic to the species, of a lethal amount of Elixir of Sulfanilamide-Massengill in man; or of diethylene glycol, the "synthetic" elixir, or Elixir of Sulfanilamide-Massengill, in animals.

V. Clinical and Pathologic Observations

By Dr. Homer A. Ruprecht and Dr. I. A. Nelson, Tulsa

(The following telegram (October 15) was received at the A. M. A. headquarters from Dr. Homer A. Ruprecht and Dr. I. A. Nelson of the Springer Clinic:)

Total of ten cases. Eight dead. One recovered. One critical. Ages from eleven months to twenty-six years. All received Elixir Sulfanilamide in amounts varying from one-half to seven ounces. Characteristic onset with nausea, vomiting, occasional diarrhea, malaise, later pain over kidney region and abdomen. All developed anuria within two to five days after beginning medication. Indications for the use of sulfanilamide were varied. Nine cases hospitalized. Characteristic physical findings were deep respirations, drowsiness, cutaneous pallor, no cyanosis, slight puffiness of face. Blood pressure normal or slightly elevated; tenderness over kidneys and upper abdomen. Three cases voided small amounts of urine which showed four plus albumin, casts and cells insignificant, no lipoids, no anemia, moderate leukocytosis, nonprotein nitrogen progress to near two hundred total, creatinine up to twelve. Patients become progressively comatose. Edema and ascites related to water administration. Death in two to seven days from onset of anuria. Postmortem findings on five cases are yellow tawny color of smooth and not enlarged liver; slight to marked purplish mottling of kidney surfaces, with severe cases showing necrosis limited to superficial portions of cortex. Inconstant peritoneal, pleural, and pericardial accumulations of clear straw colored fluid which gels. Rest of viscera insignificant. Microscopic findings show a consistent hydropic tubular nephrosis and central degeneration of liver with cells showing foamy cytoplasm. Sudan stains show (little) fatty degeneration. Consider microscopic picture similar to literature on dioxane; see Navanquez, J. Hyg. vol. 35, pages 540–548. Cannot find evidence of oxalic acid in gross nonmicroscopic tissues nor fluids. No calcium oxalate crystals.[6] Have complete viscera from one case in frozen state without fixation. Can send stained sections, portions of fixed or frozen tissues. Federal inspectors arrived today.[7]

[6] A suggestion had been telegraphed to Dr. Ruprecht October 12 that possibly there might be oxalate crystals in case the diethylene glycol contained ethylene glycol.

[7] In a letter from Dr. Ruprecht of October 11, he stated: "One of the latter two patients had received tablets of sulfanilamide over a period of two weeks without any bad effects and then changed doctors and the second doctor put him on the elixir of sulfanilamide and the typical train of symptoms followed shortly afterward."

Dr. Darwin B. Childs of Tulsa, Okla., in speaking of cases brought to his attention stated: "A patient, a 20 year old adult, who had an acute gonorrhea, took a total of 220 grains, as represented by 55 teaspoonfuls of the elixir of sulfanilamide. Twenty-four hours after the ingestion of this amount he began to have symptoms of an acute nephritis, and forty-eight hours later he was totally anuric. He died four days after receiving the last dose. The clinical picture and autopsy reports of this case closely resemble each of the other cases."

VI. Necropsies of Four Patients Following Administration of Elixir of Sulfanilamide-Massengill

O. E. Hagebusch, M. D., St. Louis

(Without knowledge of the deaths at Tulsa, Okla., Dr. O. E. Hagebusch sent the following report under date of October 19 for proposed publication in The Journal:)

In the last several days I have seen four deaths in patients using a product called "Elixir of Sulfanilamide" and sold by Massengill & Company.

These patients, all Negroes, were treated by a Dr. Weathers of East St. Louis, Ill. In all he has given the drug to about thirty people, but of the six people treated recently four are dead and have come to autopsy. One is expected to die at any time, and one may recover.

All have had similar symptoms: Vomiting and diarrhea, subnormal temperatures, slow respiration, anuria, edema of the face, hands, and feet, a progressive anemia, and then death.

All four autopsies have shown the same findings; pulmonary edema, marked nephritis with hemorrhage into the cortex of the kidney, marked hemorrhage into the pericardium, mucosa of the stomach and duodenum and into the serous surfaces of lung and liver. The liver is pale, edematous, and enlarged. Microscopic sections have not as yet been completed.

It was thought that this information should be in the hands of as many physicians as possible, and The Journal was the best means of accomplishing this end.

Reported deaths from Elixir of Sulfanilamide-Massengill

State	City	Reference number	Demise
Alabama	Arab	1	10-16-37
	Clayton	2	9-24-37
	Eufaula	3	9-20-37
	Eufaula	4	10-13-37
	Eufaula	5	10-17-37
	Headland	6	9-25-37
Arkansas	McCaskill	7	10-24-37
Georgia	Dahlonega	8	9-29-37
	Dahlonega	9	10-19-37
	Griffin	10	10-18-37
	McDonough	11	10- 6-37
	Millen	12	10-16-37
	Swainsboro	13	10-26-37
	Wadley	14	10-21-37
Illinois	East St. Louis	15	10-15-37
	East St. Louis	16	10-16-37
	East St. Louis	17	10-18-37
	East St. Louis	18	10-18-37
	East St. Louis	19	10-21-37
	East St. Louis	20	10-24-37
	Granite City	21	10-10-37
Mississippi	Cary	22	10-17-37
	Collins	23	10- 9-37
	Laurel	24	10- 5-37
	Laurel	25	10- 5-37
	Laurel	26	10-11-37
	Laurel	27	10-20-37
	Laurel	28	No date
	Philadelphia	29	10-20-37
	Magee	30	10- 5-37
	Magee	31	10-17-37
	Mount Olive	32	10- 8-37
	Mount Olive	33	10-14-37
	Mount Olive	34	10-16-37
	Mount Olive	35	10-19-37
	Mount Olive	36	10-20-37
	Mount Olive	37	10-21-37
Missouri	St. Louis	38	10-25-37
Ohio	Copley	39	
Oklahoma	Tulsa	40	
	Tulsa	41	
	Tulsa	42	
	Tulsa	43	Before 10-18-37
	Tulsa	44	
	Tulsa	45	
	Tulsa	46	
	Tulsa	47	
	Tulsa	48	

Reported deaths from Elixir of Sulfanilamide-Massengill—Continued

State	City	Reference number	Demise
South Carolina	Charleston	49	10- 4-37
	Charleston	50	10-12-37
	Charleston	51	10-13-37
	Charleston	52	10-30-37
	Charleston	53	10-30-37
Tennessee	Memphis	54	10-20-37
Texas	Madisonville	55	10-18-37
	Marlin	56	10-12-37
	Quitman	57	10-20-37
	Texas City	58	
	Wichita Falls	59	
Total deaths		[1] 59	

[1] To the best of our knowledge this list comprises the deaths confirmed by telephone, telegraph, or other authoritative communication resulting from the administration of Elixir of Sulfanilamide-Massengill up to and including October 29; no responsibility, however, is assumed for its absolute correctness. In some cases the list does not indicate the residence address of the patient but the address of the attending physician or the place of death of the victim.

Since this table was set in type, two more deaths have been reported, bringing the total up to sixty-one (November 1).

VII. Survey of Deaths

Deaths and clues of deaths were reported to the American Medical Association headquarters by various press services, by information received from physicians, and chiefly clues from the Food and Drug Administration. The latter organization placed a tremendous force of inspectors in the field. It obtained a list of approximately 700 shipments from the manufacturer. The inspectors then traced every shipment to its final designation. If the bottle had been opened, they inquired to whom it had been dispensed. It was in this manner that most of the deaths were traced after the original reports from Tulsa and East St. Louis. Each suspected case of death was then checked by the American Medical Association by telephoning or telegraphing physicians or other medical authorities. On an accompanying page is given the list of cities in which deaths occurred, the number of deaths reported to the Association to October 29, and the date on which it has been stated that the patient died. There are many additional reports not confirmed as yet.

Antidote.—On October 20 the S. E. Massengill Company sent the following telegram:

"Please wire collect by Western Union suggestion for antidote and treatment following use Elixir Sulfanilamide."

The following reply was sent:

"Antidote for Elixir Sulfanilamide-Massengill not known. Treatment presumably symptomatic."

So far as has been determined, there is no known antidote for diethylene glycol poisoning when the drug is administered in amounts comparable to that given the unfortunate victims. Telegrams were sent to Dr. E. J. Marshall, Jr., Dr. W. F. von Oettingen, and Dr. P. J. Hanzlik for suggestions. One suggested the use of gastric lavage, calcium therapy orally and intravenously, and symptomatic treatment for nephrosis. Another telegraphed: "Cannot suggest any possible antidote or treatment for patient with Elixir Sulfanilamide poisoning. Fifty percent dextrose solution with or without sodium bicarbonate intravenously might be tried." Another suggested the use of 20 percent dextrose solution intravenously to relieve renal edema if possible.

VIII. Conclusions

1. Elixir of Sulfanilamide-Massengill in the specimens examined was found to consist essentially of sulfanilamide 10 Gm in 100 cc of a solution of approximately 72 percent diethylene glycol and water 25 per cent by volume, to which had been added flavoring and coloring material.

2. Diethylene glycol in the doses given was the causative agent in deaths.

3. Pathologic results reported herewith both on animal and on man, as well as many reports received by telephone and telegram, indicate that, in cases of death following the administration of Elixir of Sulfanilamide-Massengill, anuria was present.

4. While sulfanilamide does not appear to have had any appreciable part in the toxicity of this preparation, it is well to emphasize again that sulfanilamide should be used cautiously and, until more is known of its pharmacology, should not be administered concurrently with any other substance except sodium bicarbonate (see editorial in THE JOURNAL, October 2, p. 1128, and reports by the Council on Pharmacy and Chemistry in THE JOURNAL May 29, p. 1888, and July 31, p. 358).

5. Diethylene glycol, when taken in divided does and in amount comparable to those recommended by the manufacturer for Elixir of Sulfanilamide-Massengill, is a decidedly toxic substance and cumulative poison; the pathologic picture was the same in animals that received a 75 per cent solution of diethylene glycol alone, a synthetic mixture made of 10 Gm of sulfanilamide in 100 cc of a 75 per cent solution of diethylene glycol, and the Elixir of Sulfanilamide-Massengill.

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